ClinicalEvidence

Chronic fatigue syndrome

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ABSTRACT

INTRODUCTION: Chronic fatigue syndrome (CFS) affects between 0.006% and 3% of the population depending on the criteria of definition used, with women being at higher risk than men. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for chronic fatigue syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 46 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antidepressants, cognitive behavioural therapy (CBT), corticosteroids, dietary supplements, evening primrose oil, galantamine, graded exercise therapy, homeopathy, immunotherapy, intramuscular magnesium, oral nicotinamide adenine dinucleotide, and prolonged rest.

QUESTIONS

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INTERVENTIONS

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Unknown effectiveness

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Corticosteroids . . . 24

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Nicotinamide adenine dinucleotide (oral) . . . 37

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Unlikely to be beneficial

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Likely to be ineffective or harmful

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Key points

- Chronic fatigue syndrome is characterised by severe, disabling fatigue, and other symptoms including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches.

  CFS affects between 0.006% and 3% of the population depending on the criteria used, with women being at higher risk than men.

- Graded exercise therapy has been shown to effectively improve measures of fatigue and physical functioning.

  Educational interventions with encouragement of graded exercise (treatment sessions, telephone follow-ups, and an educational package explaining symptoms and encouraging home-based exercise) improve symptoms more effectively than written information alone.

- CBT is effective in treating chronic fatigue syndrome in adults.

  CBT may also be beneficial when administered by therapists with no specific experience of chronic fatigue syndrome, but who are adequately supervised.

  In adolescents, CBT can reduce fatigue severity and improve school attendance compared with no treatment.

- We don't know how effective antidepressants, corticosteroids, and intramuscular magnesium are in treating chronic fatigue syndrome.

  Antidepressants should be considered in people with affective disorders, and tricyclics in particular have potential therapeutic value because of their analgesic properties.

- Interventions such as dietary supplements, evening primrose oil, oral nicotinamide adenine dinucleotide, homeopathy, and prolonged rest have not been studied in enough detail in RCTs for us to draw conclusions on their efficacy.

- Based on a single large RCT galantamine seems no better than placebo at improving symptoms of chronic fatigue syndrome.

- Although there is some RCT evidence that immunotherapy can improve symptoms compared with placebo, it is associated with considerable adverse effects, and should therefore probably not be offered as a treatment for chronic fatigue.

DEFINITION

Chronic fatigue syndrome (CFS) is characterised by severe, disabling fatigue, and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration, and headaches. Two widely used definitions of CFS, from the US Centers for Disease Control and Prevention (CDC; current criteria issued in 1994, which superseded the CDC criteria issued in 1988) [1] and from Oxford, UK, [2] were developed as operational criteria for research (see table 1, p 53). The principal difference between these definitions is the number and severity of symptoms, other than fatigue, that must be present. A third operational definition, the Australian criteria, is similar to the CDC diagnostic criteria, and has also been used in treatment trials. [3] The 1994 CDC criteria were reviewed with the aim of improving case ascertainment for research. [4] The exclusion criteria were clarified, and the use of specific instruments for the assessment of symptoms was recommended. [4]

INCIDENCE/ PREVALENCE

Community-based and primary-care-based studies have reported the prevalence of CFS to be from 0.007% to 2.8% in the general adult population, and from 0.006% to 3.0% in primary care, depending on the criteria used. [5]

AETIOLOGY/ RISK FACTORS

Despite considerable research effort and several hypotheses, the cause of CFS remains poorly understood. Endocrine and immunological abnormalities have been found in many people, although it is unclear whether these changes are causal, or are part of the course of the syndrome. Certain infectious illnesses, such as Epstein–Barr virus, Q fever, and viral meningitis, are associated with a greater risk of developing CFS, but many people have no evidence of viral infection, and there is no evidence of persistent infection. [6] People with prior psychiatric disorders are more likely to report with CFS later in life (OR 2.7, 95% CI 1.3 to 5.6). [7] Women are at higher risk than men (RR 1.3–1.7, depending on diagnostic criteria used; CIs not reported). [8] Population surveys in the US have found that white people have a lower risk of CFS compared with Latin Americans, African-Americans, and Native Americans. [9] [10]

PROGNOSIS

Studies have focused on people attending specialist clinics. A systematic review of studies of prognosis (search date 1996) found that children with CFS had better outcomes than adults: 54% to 94% of children showed definite improvement in symptoms (after up to 6 years' follow-up), whereas 20% to 50% of adults showed some improvement in the medium term (12–39 months) and only 6% returned to premorbid levels of functioning. [11] Despite the considerable burden of morbidity associated with CFS, we found no evidence of increased mortality. The systematic review found that a longer duration of illness, fatigue severity, comorbid depression and anxiety, and a physical attribution for CFS are factors associated with a poorer prognosis. [11] A more recent review found a median full recovery rate of 5% (range 0–31%), and the median proportion of patients who improved during follow-up to be 39.5% (range 8–63%). Good outcome was associated with less fatigue severity at baseline, a sense of control over symptoms, and not attributing the illness to a physical cause. [12]

AIMS OF INTERVENTION

To reduce levels of fatigue and associated symptoms, to increase levels of activity, and to improve quality of life.

OUTCOMES

Severity of symptoms (including **fatigue**, and **overall improvement**) and their effects on **functional status** (includes physical function, physical health, and functional impairment) and **quality of life**. There are several different instruments used to measure these outcomes, including: the medical outcomes survey short-form general health survey (SF-36, [13] a rating scale measuring quality of life, including limitation of physical functioning caused by ill health [score range 0–100, where 0 = limited in all activities and 100 = able to carry out vigorous activities], pain, energy levels, and mood); the Karnofsky scale, [14] a modified questionnaire originally developed for the rating of quality of life in people having chemotherapy for malignancy (where 0 = death and 100 = no evidence of disease); the Beck Depression Inventory, [15] a checklist for quantifying depressive symptoms (score range 0–63, where a score of 20 or more is usually considered clinically significant depression); the Hospital Anxiety and Depression scale (HADS, [16] consists of 2 subscales, each with score range 0–21, where a score of 11 or more is considered clinically significant); the Sickness Impact Profile, [17] a measure of the influence of symptoms on social and physical functioning; the Chalder Fatigue Scale, [18] a rating scale measuring subjective fatigue (score range 0–11, where scores 4 or more = excessive fatigue); the Abbreviated Fatigue Questionnaire, [19] a rating scale of subjective bodily fatigue (score range 4–28, where a lower score indicates a higher degree of fatigue); the Clinical Global Impression scale, [20] a validated measure of overall change compared with baseline at study onset (7 possible scores from "very much worse" [score 7] to "very much better" [score 1]); the Checklist Individual Strength fatigue subscale (score range 8 [no fatigue at all] to 56 [maximally fatigued]); [21] the Nottingham Health Profile, [22] with questions in 6 self-report categories: energy, pain perception, sleep patterns, sense of social isolation, emotional reactions, and physical mobility (maximum weighted score 100 [all listed complaints present], and minimum 0 [none of listed complaints present]); the Multidimensional Fatigue Inventory (MFI), [23] with 5

subscales: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation (each with a score range of 4–20, higher scores indicate higher degree of fatigue); and self-reported severity of symptoms and levels of activity; the Fatigue Severity Scale, [24] with nine 7-point subscales assessing behavioural consequences of fatigue.

METHODS

Clinical Evidence search and appraisal March 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2010, Embase 1980 to March 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 2 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language. RCTs had to be at least single blinded for drug interventions, but non-blinded studies were included for non-drug interventions. For drug interventions we excluded all studies described as "open", "open label", or not blinded. RCTs had to contain 20 or more individuals, of whom 80% or more were followed up. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 54). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments for chronic fatigue syndrome?**

OPTION **CBT**

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- CBT is effective in treating chronic fatigue syndrome in adults.
- CBT may also be beneficial when administered by therapists with no specific experience of chronic fatigue syndrome, but who are adequately supervised.
- In children and adolescents, CBT can reduce fatigue severity and improve school attendance compared with no treatment.

Benefits and harms

CBT versus control interventions:

We found one systematic review (search date 2008), [25] which included 15 RCTs in adults. The review included results from unpublished RCTs and studies that did not meet *Clinical Evidence* quality criteria in its meta-analyses, and so we have reported the results of each of the 6 published RCTs identified by the review that did meet *Clinical Evidence* inclusion criteria individually. [26] [27] [28] [29] [30] [31] We also found one additional RCT that met *Clinical Evidence* inclusion criteria, [32] which we report. This RCT is in children and adolescents and also reported on the effects of CBT on school attendance; [32] see further information on studies for full details.

Fatigue

Compared with control interventions CBT may be more effective at improving fatigue (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue severity					
[29] RCT **3-armed trial**	278 adults with CFS, CDC criteria In review [25] The remaining arm evaluated no intervention	**Improvement in fatigue severity (Checklist Individual Strength [CIS-fatigue]) , 8 months** 27/83 (33%) with CBT 10/80 (13%) with guided support See further information on studies for description of CBT and guided support	RR 2.6 for CBT *v* guided support 95% CI 1.3 to 5.0 RCT had high withdrawal rate; see further information on studies for full details	●●○	CBT
[29] RCT **3-armed trial**	278 adults with CFS, CDC criteria In review [25] The remaining arm evaluated no intervention	**Improvement in fatigue severity (self-reported) , 8 months** 42/74 (57%) with CBT 12/71 (17%) with guided support See further information on studies for description of CBT and guided support	RR 3.4 for CBT *v* guided support 95% 1.9 to 5.8 RCT had high withdrawal rate; see further information on studies for full details	●●○	CBT
[29] RCT **3-armed trial**	278 adults with CFS, CDC criteria In review [25] The remaining arm evaluated guided support	**Improvement in fatigue severity (CIS-fatigue) , 8 months** 27/83 (33%) with CBT 8/62 (13%) with no intervention See further information on studies for description of CBT and guided support	RR 2.5 for CBT *v* no intervention 95% CI 1.2 to 5.2 RCT had high withdrawal rate; see further information on studies for full details	●●○	CBT
[29] RCT **3-armed trial**	278 adults with CFS, CDC criteria In review [25] The remaining arm evaluated guided support	**Improvement in fatigue severity (self-reported) , 8 months** 42/74 (57%) with CBT 23/78 (30%) with no intervention See further information on studies for description of CBT and guided support	RR 1.9 for CBT *v* no intervention 95% CI 1.3 to 2.9 RCT had high withdrawal rate; see further information on studies for full details	●○○	CBT
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated education and support	**Change in fatigue severity (Chalder Fatigue Score)** with group CBT with usual care Absolute results not reported 103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and usual care	Difference –2.61 for group CBT *v* usual care 95% CI –4.92 to –0.30 P = 0.03	○○○	CBT
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated usual care	**Change in fatigue severity (Chalder Fatigue Score)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and education and support interventions	Difference –3.16 for group CBT *v* education and support 95% CI –5.59 to –0.74 P = 0.011	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [25] The remaining 2 arms reported on CBT plus dialysable leukocyte extract (DLE) and DLE alone	**Mean fatigue score (profile of mood states subscale) , 7 months (3 months after completion of treatment)** 16.8 with CBT plus placebo 17.3 with usual care plus placebo 43 people in the analysis CBT consisted of 6 sessions of CBT lasting 30 to 60 minutes every 2 weeks and placebo consisted of 8 biweekly injections of lyophilised normal saline	Significance not assessed		
[31] RCT **4-armed trial**	114 adults with CFS as defined by CDC criteria; baseline fatigue severity scale (FSS) scores 6.05 in people having CBT, 5.82 in people having relaxation therapy In review [25] The remaining 2 arms assessed anaerobic activity therapy and cognitive therapy	**Mean score on FSS , 12 months** 5.37 with CBT 5.62 with relaxation therapy 57 people in this analysis The population in this RCT may have been less impaired than in other similar RCTs See further information on studies for further details on study population and interventions	Significance not assessed		
[32] RCT	69 children and adolescents aged 10 to 17 years with CFS, CDC criteria	**Change in fatigue severity score (Checklist Individual Strength [CIS-fatigue]) , 5 months** –22.3 with CBT –7.6 with no intervention CBT consisted of 10 sessions over 5 months	Absolute difference 14.5 95% CI 7.4 to 21.6	○○○	CBT

No data from the following reference on this outcome. [27] [28]

Functional status

Compared with control interventions We don't know whether CBT is more effective at improving physical functioning (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[28] RCT	60 adults with CFS, CDC criteria attending a secondary-care centre In review [25]	**Predefined increase in functional score (assessed by SF-36 questionnaire) , 13 weeks** 19/30 (63%) with CBT 5/30 (17%) with relaxation CBT was given in 13 weekly sessions	RR 3.70 95% CI 2.37 to 6.31 NNT 3 95% CI 1 to 7	●●○	CBT
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25]	**Change in functional score (assessed by SF-36 questionnaire)** with group CBT with usual care	Absolute difference –1.63 for group CBT *v* usual care 95% CI –4.05 to +0.78	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated education and support	Absolute results not reported 103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and usual care			
[30] RCT **3-armed trial**	153 people with CFS, CDC criteria In review [25] The remaining arm evaluated usual care	**Change in functional score (assessed by SF-36 questionnaire)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and educational and support interventions	Absolute difference –1.23 for group CBT *v* education and support 95% CI –3.52 to +1.05	⟷	Not significant
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [25] The remaining 2 arms reported on CBT plus dialysable leukocyte extract (DLE) and DLE alone	**Mean number of non-sedentary hours , 7 months (3 months after completion of treatment)** 5.2 with CBT plus placebo 5.2 with usual care plus placebo 43 people in the analysis CBT consisted of 6 sessions of CBT lasting 30 to 60 minutes every 2 weeks and placebo consisted of 8 biweekly injections of lyophilised normal saline	Significance not assessed		
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [25] The remaining 2 arms reported on CBT plus DLE and DLE alone	**Mean score for ability to participate in daily activities (Karnofsky performance score) , 7 months (3 months after completion of treatment)** 72.1 with CBT plus placebo 73.4 with usual care plus placebo 43 people in the analysis CBT consisted of 6 sessions of CBT lasting 30 to 60 minutes every 2 weeks and placebo consisted of 8 biweekly injections of lyophilised normal saline	Significance not assessed		
[31] RCT **4-armed trial**	114 adults with CFS defined by CDC criteria; baseline physical functioning scores 46.36 in people receiving CBT, 53.77 in people receiving relaxation In review [25] The remaining 2 arms evaluated anaerobic activity therapy and cognitive therapy	**Mean score on SF-36 for physical functioning , 12 months** 58.64 with CBT 61.20 with relaxation therapy 57 people in this analysis The population in this RCT may have been less impaired than in other similar RCTs See further information on studies for further details on study population and interventions	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[32] RCT	69 children and adolescents aged 10 to 17 years with CFS, CDC criteria	**Change in functional score (assessed by short-form [SF]-36 questionnaire) , 5 months** 27.3 with CBT 10.0 with no treatment CBT consisted of 10 sessions over 5 months	Absolute difference 17.3 95% CI 6.2 to 28.4	○○○	CBT

No data from the following reference on this outcome. [27] [29]

Overall improvement

Compared with control interventions CBT may be more effective at increasing complete recovery at 5 years (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Complete recovery					
[33] RCT	53 adults with CFS, CDC criteria Further report of reference [28]	**Complete recovery , 5 years** 17/31 (55%) with CBT 7/22 (32%) with relaxation therapy	RR 1.7 95% CI 0.9 to 3.4	⟷	Not significant
[33] RCT	53 adults with CFS, CDC criteria Further report of reference [28]	**Proportion of people rating themselves as "much improved" or "very much improved" , 5 years** 17/25 (68%) with CBT 10/28 (36%) with relaxation therapy	RR 1.9 95% CI 1.1 to 3.4	●○○	CBT

No data from the following reference on this outcome. [26] [27] [29] [30] [31] [32]

Quality of life

Compared with control interventions We don't know whether CBT is more effective than usual care at improving quality of life or measures of mental health (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[27] RCT	60 adults with CFS, Oxford criteria In review [25]	**Proportion of people with a final score on Karnofsky quality-of-life scale of >80 , 12 months** 22/30 (73%) with CBT 8/30 (27%) with usual care See further information on studies for description of CBT and usual care	RR 2.75 95% CI 1.54 to 5.32 NNT 3 95% CI 2 to 5	●●○	CBT
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated education and support	**Change in quality-of-life score (assessed by short-form [SF]-36 questionnaire) , 12 months** with group CBT with usual care Absolute results not reported	Absolute difference 4.36 for group CBT *v* usual care 95% CI 0.72 to 7.97 P = 0.019	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		103 people in this analysis See further information on studies for description of CBT and usual care			
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated usual care	**Change in quality-of-life score (assessed by SF-36 questionnaire) , 12 months** with group CBT with education and support Absolute results not reported 102 people in this analysis See further information on studies for description of CBT and usual care	Absolute difference +3.16 for group CBT *v* education and support 95% CI –0.05 to +6.38 P = 0.5	⟷	Not significant
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [25] The remaining 2 arms reported on CBT plus dialysable leukocyte extract (DLE) and DLE alone	**Mean visual analogue score , 7 months (3 months after completion of treatment)** 469 with CBT plus placebo 477 with usual care plus placebo 43 people in the analysis CBT consisted of 6 sessions of CBT lasting 30 to 60 minutes every 2 weeks and placebo consisted of 8 biweekly injections of lyophilised normal saline	Significance not assessed		
Mental health					
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated education and support	**Change in mental health score (assessed by SF-36 questionnaire)** with group CBT with usual care Absolute results not reported 103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and usual care	Absolute difference 4.35 for group CBT *v* usual care 95% CI 0.72 to 7.97 P = 0.019	○○○	CBT
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated usual care	**Change in mental health score (assessed by SF-36 questionnaire)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and educational and support interventions	Absolute difference +3.16 for group CBT *v* education and support 95% CI –0.05 to +6.38 P = 0.5	⟷	Not significant
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25]	**Anxiety (assessed by Hospital Anxiety and Depression scale [HADS] score)** with group CBT	Absolute difference –1.27 for group CBT *v* usual care 95% CI –2.52 to –0.02 P = 0.045	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated education and support	with usual care Absolute results not reported 103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and usual care	Result is of borderline significance		
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated usual care	**Anxiety (assessed by HADS score)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and educational and support interventions	Absolute difference –0.51 for group CBT *v* education and support 95% CI –1.70 to +0.68	⟷	Not significant
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated education and support	**Depression (assessed by HADS score)** with group CBT with usual care Absolute results not reported 103 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and usual care	Absolute difference –0.56 for group CBT *v* usual care 95% CI –1.69 to +0.58	⟷	Not significant
[30] RCT **3-armed trial**	153 adults with CFS, CDC criteria In review [25] The remaining arm evaluated usual care	**Depression (assessed by HADS score)** with group CBT with education and support Absolute results not reported 102 people in this analysis Treatment effects at 6 and 12 months were pooled for analysis See further information on studies for description of CBT and educational and support interventions	Absolute difference –0.13 for group CBT *v* education and support 95% CI –1.13 to +0.87	⟷	Not significant

No data from the following reference on this outcome. [28] [29] [32]

Adverse effects

No data from the following reference on this outcome. [26] [27] [28] [29] [32] [30] [31]

CBT versus dialysable leukocyte extract:

We found one systematic review (search date 2005), [34] which identified one RCT evaluating CBT plus placebo versus immunological therapy (dialysable leukocyte extract, DLE) using a factorial design. [26]

Fatigue

Compared with dialysable leukocyte extract (DLE) We don't know how effective CBT is compared with DLE at improving fatigue (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms reported on CBT plus placebo and CBT plus dialysable leukocyte extract (DLE)	**Mean fatigue score (profile of mood states subscale) , 7 months (3 months after completion of treatment)** 16.8 with CBT plus placebo 16.9 with DLE 46 people in the analysis Treatment consisted of 6 sessions of CBT biweekly and 8 biweekly injections of placebo (lyophilised normal saline) or no CBT and 8 biweekly injections of DLE	Significance not assessed		

Functional status

Compared with dialysable leukocyte extract (DLE) We don't know how effective CBT is compared with DLE at improving functional status (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Functional status					
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms reported on CBT plus placebo and CBT plus dialysable leukocyte extract (DLE)	**Mean number of non-sedentary hours , 7 months (3 months after completion of treatment)** 5.2 with CBT plus placebo 4.9 with DLE 46 people in the analysis Treatment consisted of 6 sessions of CBT biweekly and 8 biweekly injections of placebo (lyophilised normal saline) or no CBT and 8 biweekly injections of DLE	Significance not assessed		
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms evaluated CBT plus placebo and CBT plus DLE	**Mean score for ability to participate in daily activities (Karnofsky performance score) , 7 months (3 months after completion of treatment)** 72.1 with CBT plus placebo 74.8 with dialysable leukocyte extract (DLE) 46 people in the analysis Treatment consisted of 6 sessions of CBT biweekly and 8 biweekly injections of placebo (lyophilised normal saline) or no CBT and 8 biweekly injections of DLE	Statistical significance not reported		

Overall improvement

No data from the following reference on this outcome. [26] [34]

Quality of life

Compared with dialysable leukocyte extract (DLE) We don't know how effective CBT is compared with DLE at improving quality of life (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms reported on CBT plus placebo and CBT plus dialysable leukocyte extract (DLE)	**Mean visual analogue score , 7 months (3 months after completion of treatment)** 469 with CBT plus placebo 498 with DLE 46 people in the analysis Treatment consisted of 6 sessions of CBT biweekly and 8 biweekly injections of placebo (lyophilised normal saline) or no CBT and 8 biweekly injections of DLE	Significance not assessed		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[26] RCT **4-armed trial**	90 adults with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms reported on CBT plus placebo and CBT plus dialysable leukocyte extract (DLE)	**Number of people with minor discomfort at injection site (with 1 or more injection) , 7 months (3 months after completion of treatment)** with CBT plus placebo with DLE Absolute results not reported Treatment consisted of 6 sessions of CBT biweekly and 8 biweekly injections of placebo (lyophilised normal saline) or no CBT and 8 biweekly injections of DLE	Adverse effects data pooled from all 4 trial arms for all who received DLE (45 people) versus all who received placebo (43 people). Significantly more people suffered minor discomfort at the injection site with DLE than with placebo. No adverse effects data for CBT reported	○○○	DLE

Further information on studies

[27] The active treatment consisted of a cognitive behavioural assessment, followed by 16 weekly sessions of behavioural experiments, problem-solving activity, and re-evaluation of thoughts and beliefs that inhibited a return to normal functioning. The control was usual general-practice care in people attending a secondary-care centre.

[29] **Interventions** CBT consisted of 16 sessions over 8 months administered by 13 therapists with no previous experience of treating CFS. The guided-support groups were similar to CBT in terms of treatment schedule, with people receiving non-directive support from a social worker. **Loss to follow-up** This multicentre RCT had a high withdrawal rate (25% after 8 months), especially in the CBT and guided-support groups. Although the

presented confidence intervals are not adjusted for multiple comparisons, the results would remain significant after any reasonable adjustment. The authors commented that the results were similar after intention-to-treat analysis, but these results were not presented.

[30] CBT (52 people) consisted of 8 sessions over 16 weeks administered by experienced therapists. The education and support group (50 people) met the same therapists as those with CBT, in the same setting, for the same duration, and were taught a different relaxation exercise each week. The usual-care group (51 people) was managed in primary care and only attended the hospital for assessment at baseline and at 6 and 12 months. No adjustments were made for the multiple number of statistical tests carried out.

[31] CBT (29 people) consisted of thirteen 45-minute sessions over 26 weeks administered by experienced therapists. Relaxation treatment (28 people) comprised a combination of progressive muscle relaxation, stretching, autogenic training, and breathing focus techniques over 26 weeks and each biweekly session also lasted 45 minutes. Both of the interventions were individualised for different participants (not further defined). The RCT also reported that the study population at baseline was less physically impaired, more likely to be employed, and less likely to have psychiatric co-morbidities than some of the previous similar RCTs in this area, and this may explain the difference in the results between RCTs.

[32] The RCT found that CBT significantly improved school attendance at 5 months (% change in school attendance: 28% with CBT *v* 10% with no treatment; difference 18%, 95% CI 0.8% to 35.5%). A follow-up study (mean duration 2.1 years) of the RCT assessed 66/69 (96%) of the original trial participants. At the end of the trial, all participants were offered CBT: of the 34 people originally assigned waiting list control, 18 received CBT. The analysis therefore compared outcomes in 50 people treated with CBT (32 people initially randomised to CBT plus 18 people initially randomised to waiting list control who subsequently received CBT) with outcomes in the 16 people who refused CBT and thus received no treatment. The follow-up study found that, irrespective of the group to which they were randomised in the initial RCT, people receiving CBT were significantly less fatigued (P = 0.009), had significantly higher physical functioning as measured on the short-form (SF)-36 physical functioning subscale (P = 0.07), and had significantly improved school/work attendance (P = 0.002) at a mean 2 years than people given no intervention. [35]

Comment:

A randomised trial comparing CBT and non-directive counselling found that both interventions were of benefit in the management of people who consulted their family doctor because of fatigue symptoms. [36] In this study, 28% of the sample conformed to CDC criteria for CFS.

We found one RCT (171 people, CDC criteria) comparing a minimal intervention based on CBT (comprising a self-instruction booklet with information about CFS and weekly assignments) versus a waiting list control. [37] The intervention lasted at least 16 weeks and included email or phone contact with an experienced therapist every 2 weeks. The RCT found that guided self-instructions significantly reduced fatigue as measured by the Checklist Individual Strength (CIS) fatigue severity subscale compared with waiting list control at 6 to 12 months. The RCT also found that a greater proportion of those receiving self-instructions had a clinically significant improvement (CIS fatigue severity <35) compared with waiting list controls and the self-instruction group also scored significantly higher on the SF-36 physical function subscale compared with the control group at 6 to 12 months.

Clinical guide:

There is moderate evidence of benefit of CBT in CFS. The effectiveness of CBT for CFS outside specialist settings has been questioned. The results of the multicentre RCT [29] suggest that CBT may be effective when administered by less-experienced therapists with adequate supervision.

OPTION GRADED EXERCISE THERAPY

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- Graded exercise therapy has been shown to effectively improve measures of fatigue and physical functioning.
- Educational interventions with encouragement of graded exercise (treatment sessions, telephone follow-ups, and an educational package explaining symptoms and encouraging home-based exercise) improve symptoms more effectively than written information alone.

Benefits and harms

Graded exercise therapy versus control interventions:

We found two systematic reviews (search dates 2004 [38] and 2005 [34]). The first systematic review [38] included the results of an unpublished RCT in its meta-analyses, and so we have reported the results of the three published

RCTs identified by the review individually. [39] [40] [41] The second systematic review [34] did not perform a meta-analysis or report quantified results from each study, and identified one additional RCT not included in the first systematic review. [42]

Fatigue

Compared with control intervention Graded aerobic exercise programmes seem more effective at improving measures of fatigue compared with flexibility training and relaxation training or general advice (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[39] RCT	66 people with CFS, Oxford criteria In review [38]	**Mean change in Chalder Fatigue Score , 12 weeks** –8.4 with graded exercise –3.1 with control intervention (flexibility and relaxation training) See further information on studies for description of exercise intervention and relaxation training	P = 0.004	○○○	graded exercise therapy
[40] RCT **4-armed trial**	136 people with CFS, Oxford criteria In review [38] Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine	**Proportion of people with Chalder Fatigue Score <4 , 26 weeks** 12/67 (18%) with graded exercise, with or without fluoxetine 4/69 (6%) with general advice, with or without fluoxetine Data pooled for graded exercise groups and for general advice groups See further information on studies for description of graded exercise and general advice	RR 3.10 95% CI 1.05 to 9.10 NNT 9 95% CI 5 to 91	●●○	graded exercise therapy
[41] RCT	61 people with CFS, CDC criteria In review [38]	**Mean change in Chalder Fatigue Score for physical fatigue , 12 weeks** 3.5 with graded exercise 1.8 with control intervention (flexibility and relaxation training) See further information on studies for description of exercise intervention and relaxation training Fatigue measured using 14-item version of Chalder scale; 8 items for physical fatigue (0–8)	P = 0.07	⟷	Not significant
Mental fatigue					
[41] RCT	61 people with CFS, CDC criteria In review [38]	**Mean change in Chalder Fatigue Score for mental fatigue , 12 weeks** 1.8 with graded exercise 0.8 with control intervention (flexibility and relaxation training) See further information on studies for description of exercise intervention and relaxation training Fatigue measured using 14-item version of Chalder scale; 6 items for mental fatigue (0–6)	P = 0.02	○○○	graded exercise therapy

No data from the following reference on this outcome. [42]

Functional status

Compared with control intervention Graded aerobic exercise programmes may be more effective at improving measures of physical functioning compared with flexibility training and relaxation training or general advice (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[39] RCT	66 people with CFS, Oxford criteria In review [38]	**Mean change in short-form (SF)-36 physical function score , 12 weeks** 20.5 with graded exercise 8.0 with control intervention (flexibility and relaxation training) See further information on studies for description of exercise intervention and relaxation training	P = 0.01	○○○	graded exercise therapy

No data from the following reference on this outcome. [40] [41] [42]

Overall improvement

Compared with control interventions Graded exercise therapy may lead to greater overall improvement in symptoms compared with control interventions (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[39] RCT	66 people with CFS, Oxford criteria In review [38]	**Proportion of people who reported feeling "much better" or "very much better" on Clinical Global Impression Scale , 12 weeks** 52% with graded aerobic exercise 27% with control intervention (flexibility and relaxation training) Absolute numbers not reported See further information on studies for description of exercise intervention and relaxation training	P = 0.04	○○○	graded exercise therapy
[41] RCT	61 people with CFS, CDC criteria In review [38]	**Proportion of people with self-rated improvement with Clinical Global Impression Scale , 12 weeks** 29/32 (91%) with graded exercise 22/29 (76%) with control intervention (flexibility and relaxation training) See further information on studies for description of exercise intervention and relaxation training	P = 0.23	⟷	Not significant
[42] RCT	49 people with CFS, CDC criteria In review [34]	**Proportion of people who reported feeling "much better" or "very much better" in a self-reported rating of improvement , 12 weeks** 48% with graded exercise 21% with standard medical care Absolute numbers not reported	P = 0.05	○○○	graded exercise therapy

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Graded exercise was defined as increased activity to 30 minutes of exercise 5 times a week up to an energy expenditure of 70% of VO_2 max			

No data from the following reference on this outcome. [40]

Quality of life

Compared with control interventions Graded exercise therapy may be more effective at improving depressive symptoms but not anxiety symptoms (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mental health					
[41] RCT	61 people with CFS, CDC criteria In review [38]	**Self-reported anxiety symptoms (mean change in Hospital Anxiety and Depression scale [HADS] anxiety score) , 12 weeks** 1.6 with graded exercise 0.9 with control intervention (flexibility and relaxation training) See further information on studies for description of exercise intervention and relaxation training	P = 0.2	⟷	Not significant
[41] RCT	61 people with CFS, CDC criteria In review [38]	**Self-reported depressive symptoms (mean change in HADS depression score) , 12 weeks** 1.7 with graded exercise 0.6 with control intervention (flexibility and relaxation training) See further information on studies for description of exercise intervention and relaxation training	P = 0.04	○○○	exercise

No data from the following reference on this outcome. [39] [40] [42]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal rates					
[40] RCT **4-armed trial**	136 people with CFS, Oxford criteria In review [38] Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo,	**Withdrawal rates** 25/68 (37%) with graded exercise, with or without fluoxetine 15/69 (22%) with general advice, with or without fluoxetine Reasons for withdrawal were not reported Data pooled for graded exercise groups and for general advice groups	RR 1.70 95% CI 0.98 to 2.90	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	and general advice plus fluoxetine	See further information on studies for description of graded exercise and general advice			

No data from the following reference on this outcome. [39] [41] [42]

Graded exercise therapy plus education versus written information alone:

We found one systematic review (search date 2004). [38] The review identified one RCT comparing three types of educational intervention plus encouragement of graded exercise versus only written information (control group). [43]

Fatigue

Graded exercise therapy plus education compared with written information alone An educational package to encourage graded exercise is more effective at improving measures of fatigue at 1 year than written information alone (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[43] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [38] The remaining arms evaluated telephone intervention graded exercise and maximum intervention graded exercise	**Mean Chalder Fatigue Score (scale range: 0–11; a score >3 indicates excessive fatigue) , 1 year** 3.2 with minimum intervention graded exercise 10.6 with written information See further information on studies for description of the 3 educational interventions	P <0.001 for minimum intervention graded exercise *v* control	○○○	graded exercise therapy plus education
[43] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [38] The remaining arms evaluated minimum intervention graded exercise and maximum intervention graded exercise	**Mean Chalder Fatigue Score (scale range: 0–11; a score >3 indicates excessive fatigue) , 1 year** 3.5 with telephone intervention graded exercise 10.6 with written information See further information on studies for description of the 3 educational interventions	P <0.001 for telephone intervention graded exercise *v* control	○○○	graded exercise therapy plus education
[43] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [38] The remaining arms evaluated minimum intervention graded exercise and telephone intervention graded exercise	**Mean Chalder Fatigue Score (scale range: 0–11; a score >3 indicates excessive fatigue) , 1 year** 3.1 with maximum intervention graded exercise 10.6 with written information See further information on studies for description of the 3 educational interventions	P <0.001 for maximum intervention graded exercise *v* control	○○○	graded exercise therapy plus education

Functional status

Graded exercise therapy plus education compared with written information alone An educational package to encourage graded exercise is more effective at improving measures of physical functioning at 1 year than written information alone (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[43] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [38] The remaining arms evaluated telephone intervention graded exercise and maximum intervention graded exercise	**Mean short-form (SF)-36 physical functioning score (score range: 10–30, where 10 = maximum impairment and 30 = no impairment) , 1 year** 25.1 with minimum intervention graded exercise 16.9 with written information See further information on studies for description of the 3 educational interventions	P <0.001 for minimum intervention graded exercise *v* control	○○○	graded exercise therapy plus education
[43] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [38] The remaining arms evaluated minimum intervention graded exercise and maximum intervention graded exercise	**Mean SF-36 physical functioning score (score range: 10–30, where 10 = maximum impairment and 30 = no impairment) , 1 year** 24.3 with telephone intervention graded exercise 16.9 with written information See further information on studies for description of the 3 educational interventions	P <0.001 for telephone intervention graded exercise *v* control	○○○	graded exercise therapy plus education
[43] RCT **4-armed trial**	148 people with CFS, Oxford criteria In review [38] The remaining arms evaluated minimum intervention graded exercise and telephone intervention graded exercise	**Mean SF-36 physical functioning score (score range: 10–30, where 10 = maximum impairment and 30 = no impairment) , 1 year** 24.9 with maximum intervention graded exercise 16.9 with written information See further information on studies for description of the 3 educational interventions	P <0.001 for maximum intervention graded exercise *v* control	○○○	graded exercise therapy plus education

Overall improvement

No data from the following reference on this outcome. [43]

Quality of life

No data from the following reference on this outcome. [43]

Adverse effects

No data from the following reference on this outcome. [43]

Further information on studies

[39] Everyone had individual weekly sessions supervised by an exercise physiologist. People in the aerobic-exercise group built up their level of activity to 30 minutes of exercise a day (walking, cycling, swimming up to a maximum oxygen consumption of 60% of VO_2 max). People in the flexibility and relaxation training group were taught stretching and relaxation techniques (maximum 30 minutes daily, 5 days/week) and were specifically told to avoid any extra physical activities.

[40] The graded-exercise groups were given specific advice to do preferred aerobic exercise (such as walking, jogging, swimming, or cycling) for 20 minutes three times a week up to an energy expenditure of 75% of VO_2 max. People in the general-advice groups were not given any specific advice on frequency, intensity, or duration of aerobic activity.

[41] Graded activity consisted of aerobic exercise (walking, swimming, or cycling) for up to 15 minutes every second day. Intensity of activity was determined by mean heart rate during exercise. If there was a worsening of symptoms, the next exercise session was shortened or cancelled, and subsequent sessions reduced to a length considered by the participant to be manageable. People in the relaxation and flexibility group listened to a relaxation tape and performed stretching exercises every second day.

[43] People in the three educational-intervention groups received a minimum intervention consisting of two treatment sessions, two telephone follow-ups, and an educational package that provided an explanation of symptoms and encouraged home-based exercise. One group received the minimum intervention; one group received 7 additional follow-up telephone calls (telephone intervention); and another received 7 additional face-to-face sessions over 4 months (maximum intervention). People in the written-information group received advice and an information booklet that encouraged graded activity, but gave no explanation for the symptoms.

Comment: **Clinical guide:**
There is good evidence of benefit for graded exercise therapy in CFS. However, experience suggests that CFS symptoms may be exacerbated by overly ambitious or overly hasty attempts at exercise.

OPTION ANTIDEPRESSANTS

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- We don't know how effective antidepressants are in treating chronic fatigue syndrome.
- Antidepressants should be considered in people with affective disorders, and tricyclics in particular have potential therapeutic value because of their analgesic properties.

Benefits and harms

Fluoxetine versus placebo:

We found one systematic review (search date 2005), [34] which did not conduct a meta-analysis or report quantified results from each study. The systematic review [34] identified two RCTs. [44] [40]

Fatigue

Fluoxetine compared with placebo Fluoxetine is no more effective at improving fatigue (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[44] RCT	107 depressed and non-depressed people with CFS, Oxford criteria In review [34]	**Mean scores on subscale of Checklist Individual Strength , 8 weeks** with fluoxetine with placebo Absolute results not reported	Mean difference –0.16 95% CI –0.64 to +0.31	⟷	Not significant
[40] **4-armed trial**	136 people with CFS, Oxford criteria In review [34]	**Fatigue severity , 12 weeks** with fluoxetine with placebo Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine	Combined analysis: results pooled for fluoxetine groups and for placebo groups			

Quality of life

Fluoxetine compared with placebo Fluoxetine may be more effective at improving symptoms of anxiety and depression (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Depression					
[44] RCT	107 depressed and non-depressed people with CFS, Oxford criteria In review [34]	**Improvement in the Beck Depression Inventory , 8 weeks** with fluoxetine with placebo Absolute results not reported	Mean difference –0.19 95% CI –0.35 to –0.02 The difference is small, and possibly not clinically important	○○○	fluoxetine
[40] **4-armed trial**	136 people with CFS, Oxford criteria In review [34] Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine	**Mean change in Hospital Anxiety and Depression scale (HADS) score , 12 weeks** with fluoxetine with placebo Absolute results not reported Combined analysis: results pooled for fluoxetine groups and for placebo groups	Mean difference 1.10 95% CI 0.03 to 2.20	○○○	fluoxetine

Functional status

No data from the following reference on this outcome. [40] [44]

Overall improvement

No data from the following reference on this outcome. [40] [44]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[44] RCT	107 depressed and non-depressed people with CFS, Oxford criteria In review [34]	**Withdrawal rates owing to adverse effects** 9/54 (17%) with fluoxetine 2/53 (4%) with placebo	Reported as not significant P value not reported	⟷	Not significant
[40] RCT **4-armed trial**	136 people with CFS, Oxford criteria In review [34] Interventions compared were graded aerobic exercise plus placebo, graded aerobic exercise plus fluoxetine, general advice plus placebo, and general advice plus fluoxetine	**Withdrawal rates** 24/68 (36%) with fluoxetine 16/69 (24%) with placebo Combined analysis: results pooled for fluoxetine groups and for placebo groups	Significance not assessed		
Adverse effects					
[44] RCT	107 depressed and non-depressed people with CFS, Oxford criteria In review [34]	**Tremor , 8 weeks** with fluoxetine with placebo	P = 0.006	○○○	placebo
[44] RCT	107 depressed and non-depressed people with CFS, Oxford criteria In review [34]	**Perspiration , 8 weeks** with fluoxetine with placebo	P = 0.008	○○○	placebo

Phenelzine versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT. [45]

Overall improvement

Phenelzine compared with placebo Phenelzine may be more effective at improving symptoms of chronic fatigue syndrome (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[45] RCT	30 people with CFS, CDC 1988 criteria In review [34]	**Overall improvement , 6 weeks** with phenelzine with placebo Absolute results not reported The RCT assessed various outcomes using a modified Karnofsky scale and other outcome measures (including functional status questionnaire, profile of mood states, Centres for Epidemiological Study of Depression fatigue severity scale, and symptom severity checklist)	Significance not assessed for individual measures reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT concluded that there was a pattern of improvement across several measures with phenelzine compared with placebo			

Fatigue

No data from the following reference on this outcome. [45]

Functional status

No data from the following reference on this outcome. [45]

Quality of life

No data from the following reference on this outcome. [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal because of adverse effects					
[45] RCT	30 people with CFS, CDC 1988 criteria In review [34]	**Withdrawal because of adverse effects , 6 weeks** 3/15 (20%) with phenelzine 0/15 (0%) with placebo	Significance not assessed		

Moclobemide versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT. [46]

Overall improvement

Moclobemide compared with placebo Moclobemide is no more effective at improving symptoms of chronic fatigue (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[46] RCT	90 people with CFS, Australian criteria In review [34]	**Proportion of people reporting improvement on self-reported global improvement scale , 6 weeks** 24/47 (51%) with moclobemide (450–600 mg/day)	OR 2.16 95% CI 0.90 to 5.10	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		14/43 (33%) with placebo			
[46] RCT	90 people with CFS, Australian criteria In review [34]	**Standardised improvement on Karnofsky scale , 6 weeks** 0.86 with moclobemide (450–600 mg/day) 0.58 with placebo	Mean difference +0.28 95% CI –0.2 to +0.8	⟷	Not significant

Fatigue

No data from the following reference on this outcome. [46]

Functional status

No data from the following reference on this outcome. [46]

Quality of life

No data from the following reference on this outcome. [46]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal because of adverse effects					
[46] RCT	90 people with CFS, Australian criteria In review [34]	**Withdrawal because of adverse effects , 6 weeks** 7/47 (15%) with moclobemide (450–600 mg/day) 6/43 (14%) with placebo	Significance not assessed		
Adverse effects					
[46] RCT	90 people with CFS, Australian criteria In review [34]	**Adverse effects , 6 weeks** with moclobemide (450–600 mg/day) with placebo Reported adverse effects were agitation (5 people), headache (2 people), insomnia (6 people), gastrointestinal problems (5 people), malaise (4 people), and anxiety (3 people) Individual adverse effects according to treatment group not reported			

Sertraline versus clomipramine:
We found one RCT. [47]

Overall improvement

Sertraline compared with clomipramine Sertraline is no more effective at improving symptoms of chronic fatigue (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[47] RCT	40 people with CFS	**Mean % improvement from baseline in the Clinical Global Impression scale** 31.8% with sertraline 20.7% with clomipramine	P = 0.28	⟷	Not significant

Fatigue

No data from the following reference on this outcome. [47]

Functional status

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

Further information on studies

Comment:

Fluoxetine versus placebo:
The first RCT [44] used a shorter duration of treatment and studied people with a longer duration of illness compared with the second RCT. [40]

Adverse effects
The FDA and other regulatory bodies have issued a number of alerts and revised prescribing information regarding the use of antidepressants — in particular relating to the increased risk of self-

harm and suicide. [48] See reviews on depression in adults and depression in children and adolescents.

Clinical guide:
Although antidepressants have not been shown in RCTs to be of significant benefit, their use should be considered in people with depressive disorders. Tricyclic antidepressants have analgesic properties and may also be of benefit in people complaining of insomnia.

OPTION CORTICOSTEROIDS

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- We don't know how effective corticosteroids are in treating chronic fatigue syndrome.

Benefits and harms

Fludrocortisone versus placebo:

We found one systematic review (search date 2005), [34] which did not conduct a meta-analysis or report quantified results from each study. The review [34] identified two RCTs. [49] [50]

Fatigue

Fludrocortisone compared with placebo Fludrocortisone seems no more effective at improving measures of fatigue (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[50] RCT **Crossover design**	25 people with CFS, CDC criteria In review [34]	**Mean change in fatigue severity visual analogue scale (VAS) score , 6 weeks** 0.1 with fludrocortisone 0.4 with placebo	P = 0.37 Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover	⟷	Not significant

No data from the following reference on this outcome. [49]

Overall improvement

Fludrocortisone compared with placebo Fludrocortisone seems no more effective at improving symptoms of chronic fatigue syndrome (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[49] RCT	100 people with neurally mediated hypotension and CFS, CDC criteria In review [34]	**Proportion of people with an improvement of at least 15 points on a self-reported global scale of "wellness" (scale of 1–100) , 9 weeks** 14% with fludrocortisone (titrated to 0.1 mg/day) 10% with placebo Absolute numbers not reported The RCT determined *a priori* that an improvement of at least 5 points on a self-rated 100-point global scale of "wellness" was a meaningful change	P = 0.76	⟷	Not significant

No data from the following reference on this outcome. [50]

Functional status

Fludrocortisone compared with placebo Fludrocortisone seems no more effective at improving measures of physical functioning (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[50] RCT **Crossover design**	25 people with CFS, CDC criteria In review [34]	**Mean change in short-form (SF)-36 physical functioning score , 6 weeks** +6.5 with fludrocortisone –1.6 with placebo	P = 0.15 Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover	⟷	Not significant

No data from the following reference on this outcome. [49]

Quality of life

No data from the following reference on this outcome. [49] [50]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[49] RCT	100 people with neurally mediated hypotension and CFS, CDC criteria In review [34]	**Withdrawal because of adverse effects , 9 weeks** 12/50 (24%) with fludrocortisone (titrated to 0.1 mg/day) 4/50 (8%) with placebo	RR 3.00 95% CI 1.04 to 8.67 NNH 6 95% CI 3 to 8	●●○	placebo
[50] RCT **Crossover design**	25 people with CFS, CDC criteria In review [34]	**Withdrawal rate** 3 people with fludrocortisone 1 person with placebo People receiving fludrocortisone withdrew because of worsening CFS symptoms (fatigue, headache, or insomnia) The person withdrew from the placebo group to have scheduled ovarian surgery	Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover		

Hydrocortisone versus placebo:

We found one systematic review (search date 2005), [34] which did not conduct a meta-analysis or report quantified results from each study. The review [34] identified two RCTs. [51] [52]

Fatigue

Hydrocortisone compared with placebo Hydrocortisone may be more effective at improving overall symptoms of chronic fatigue (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[52] RCT **Crossover design**	32 people with CFS, Oxford criteria In review [34]	**Mean change in fatigue score from baseline (patient-assessed 11-item scale, overall score 0–33, higher score indicates greater fatigue) , 1 month** –6.7 with hydrocortisone (5 or 10 mg/day) –2.4 with placebo Absolute numbers not reported Allocated treatments were given for 4 weeks Pre-crossover results	Significance not assessed Benefit from hydrocortisone may be short-term; see further information on studies for full details		

No data from the following reference on this outcome. [51]

Functional status

Hydrocortisone compared with placebo Hydrocortisone seems no more effective at improving functional status (as assessed by activity scale and Sickness Impact Profile) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Functional status					
[51] RCT	65 people with CFS, CDC 1998 criteria In review [34]	**Change in activity scale (change from baseline) , 12 weeks** 0.3 with hydrocortisone (25–35 mg/day) 0.7 with placebo Allocated treatments were given for 12 weeks	P = 0.32	⟷	Not significant
[51] RCT	65 people with CFS, CDC 1998 criteria In review [34]	**Change in Sickness Impact Profile (change from baseline) , 12 weeks** –2.5 with hydrocortisone (25–35 mg/day) –2.2 with placebo Allocated treatments were given for 12 weeks	P = 0.85	⟷	Not significant

No data from the following reference on this outcome. [52]

Overall improvement

Hydrocortisone compared with placebo Hydrocortisone may be more effective at improving overall symptoms of chronic fatigue (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[51] RCT	65 people with CFS, CDC 1998 criteria In review [34]	**Proportion of people with improvement of at least 5 points on self-rated 100-point scale , 12 weeks**	P = 0.04 Clinical significance of this difference is unclear	◌◌◌	hydrocortisone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		53% with hydrocortisone (25–35 mg/day) 29% with placebo Absolute numbers not reported Allocated treatments were given for 12 weeks			

No data from the following reference on this outcome. [52]

Quality of life

Hydrocortisone compared with placebo Hydrocortisone seems no more effective at improving depressive symptoms (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Depression					
[51] RCT	65 people with CFS, CDC 1998 criteria In review [34]	**Change in Beck Depression Inventory (change from base-line) , 12 weeks** –2.1 with hydrocortisone (25–35 mg/day) –0.4 with placebo Allocated treatments were given for 12 weeks	P = 0.17	⟷	Not significant

No data from the following reference on this outcome. [52]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[51] RCT	65 people with CFS, CDC 1998 criteria In review [34]	**Adverse effects** with hydrocortisone (25–35 mg/day) with placebo 12 people (40%) taking hydrocor-tisone experienced adrenal sup-pression (assessed by measuring cortisol levels) Allocated treatments were given for 12 weeks			
[52] RCT **Crossover design**	32 people with CFS, Oxford crite-ria In review [34]	**Adverse effects** with hydrocortisone (5 or 10 mg/day) with placebo The RCT reported minor adverse effects in up to 10% of people taking hydrocortisone: 3 people taking hydrocortisone had exacer-bation of acne and nervousness			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		1 person taking placebo had an episode of fainting Allocated treatments were given for 4 weeks Pre-crossover results			

Hydrocortisone plus fludrocortisone versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT. [53]

Fatigue

Hydrocortisone plus fludrocortisone compared with placebo Combined treatment with hydrocortisone plus fludrocortisone may be no more effective than placebo at improving fatigue (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[53] RCT **Crossover design**	100 people with CFS, CDC criteria In review [34]	**Mean visual analogue scale (VAS) fatigue score (0 = no fatigue to 10 = severe fatigue) , 3 months** 6.6 with hydrocortisone 5 mg daily plus fludrocortisone 50 micrograms daily 6.7 with placebo Pre-crossover results not reported No washout period between treatments; see comment Treatments were given for 3 months	P = 0.76 Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover	⟷	Not significant
[53] RCT **Crossover design**	100 people with CFS, CDC criteria In review [34]	**Mean score on Abbreviated Fatigue Questionnaire , 3 months** 8 with hydrocortisone 5 mg daily plus fludrocortisone 50 micrograms daily 7 with placebo Pre-crossover results not presented No washout period between treatments; see comment Treatments were given for 3 months	P = 0.69 Results should be interpreted with caution, as it is possible that treatment effects may persist after crossover	⟷	Not significant

Functional status

No data from the following reference on this outcome. [53]

Overall improvement

No data from the following reference on this outcome. [53]

Quality of life

No data from the following reference on this outcome. [53]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT **Crossover design**	100 people with CFS, CDC criteria In review [34]	**Adverse effects** with hydrocortisone 5 mg daily plus fludrocortisone 50 micrograms daily with placebo 2 people withdrew because of concerns about the effect of corticosteroids 1 person withdrew because of adverse effects (acne and weight gain) of hydrocortisone plus fludrocortisone treatment Pre-crossover results not presented No washout period between treatments; see comment Treatments were given for 3 months			

Further information on studies

[50] The RCT found no significant difference between fludrocortisone and placebo in change in myalgia score (assessed using a visual analogue scale [VAS] from 0 [no problem] to 10 [could not be worse]: –0.3 with fludrocortisone *v* +1.1 with placebo; P = 0.53); concentration (change in concentration score: –0.9 with fludrocortisone *v* –0.3 with placebo; P = 0.4); joint pain (change in joint pain score: –0.3 with fludrocortisone *v* 0.8 with placebo; P = 0.15); or social functioning (change in social functioning: 6.5 with fludrocortisone *v* 0.0 with placebo; P = 0.3).

[52] The crossover RCT found that, although fatigue decreased with low-dose hydrocortisone, fatigue increased within 28 days of crossover into the placebo group. [52] Therefore, any benefit from low-dose hydrocortisone may be short-lived, whereas higher doses are associated with adverse effects.

Comment: The RCTs used different reasons for their choice of active treatment. The use of fludrocortisone, a mineralocorticoid, was based on the hypothesis that CFS is associated with neurally mediated hypotension. [54] The use of hydrocortisone, a glucocorticoid, in the other RCTs was based on evidence of underactivity of the hypothalamic–pituitary–adrenocortical axis in some people with CFS. [55]

Clinical guide:
There is weak evidence of benefit for low-dose hydrocortisone; however, benefit may be short-lived, and higher doses are associated with adverse effects.

OPTION DIETARY SUPPLEMENTS

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- Dietary supplements have not been studied in enough detail for us to draw conclusions on their efficacy.

Benefits and harms

Dietary supplements versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT. [56] We found two subsequent RCTs. [57] [58]

Fatigue

Compared with placebo Dietary supplements may be no more effective at improving fatigue at 8 to 14 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[56] RCT	People with CFS, number of people not reported In review [34]	**Change in Checklist Individual Strength fatigue subscale (CIS-fatigue) from baseline , 10 weeks** From 51.4 to 48.6 with polynutrient supplement (containing several vitamins, minerals, and coenzymes, taken twice daily) From 51.3 to 48.2 with placebo Allocated treatments were given for 10 weeks	Difference +2.16 95% CI –4.30 to +4.39	⟷	Not significant
[57] RCT	71 people with CFS, CDC criteria and 2 or more of: tender lymph nodes, sore throat, or poor temperature control	**Change in Chalder physical fatigue subscale from baseline , 8 weeks** –1.5 with food supplements (Bio-Bran MGN-3) –1.8 with placebo Treatments were given for 8 weeks	Difference –0.3 95% CI –3.2 to +2.6 P = 0.84	⟷	Not significant
[58] RCT	57 people with CFS, CDC criteria	**Fatigue severity as measured by Checklist Individual Strength fatigue subscale (CIS-fatigue) , 14 weeks** with food supplement (acclydine) with placebo Absolute results not reported Treatments were given for 14 weeks	Difference +1.1 95% CI –4.4 to +6.5 P = 0.70	⟷	Not significant

Functional status

Compared with placebo Dietary supplements may be no more effective at improving functional status (as assessed by the Sickness Impact Profile) at 10 to 14 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Functional status					
[56] RCT	People with CFS, number of people not reported	**Proportion of people with Sickness Impact Profile (SIP) score <750 , 10 weeks**	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [34]	4% with polynutrient supplement (containing several vitamins, minerals, and coenzymes, taken twice daily) 12% with placebo Absolute numbers not reported Allocated treatments were given for 10 weeks			
[58] RCT	57 people with CFS, CDC criteria	**Functional impairment (assessed by the Sickness Impact Profile [SIP]-8) , 14 weeks** with food supplement (acclydine) with placebo Absolute results not reported Treatments were given for 14 weeks	Difference +59.1 95% CI –201.7 to +319.8 P = 0.65	⟷	Not significant

No data from the following reference on this outcome. [57]

Overall improvement

No data from the following reference on this outcome. [56] [57] [58]

Quality of life

No data from the following reference on this outcome. [56] [57] [58]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[56] RCT	People with CFS, number of people not reported In review [34]	**Withdrawal rate** with polynutrient supplement (containing several vitamins, minerals, and coenzymes, taken twice daily) with placebo 3 people (11%) on active treatment withdrew from the RCT because of nausea			
Adverse effects (general)					
[57] RCT	71 people with CFS, CDC criteria and 2 or more of: tender lymph nodes, sore throat, or poor temperature control	**Adverse effects** with food supplements (BioBran MGN-3) with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		3 people on active treatment withdrew because of mild nausea, an exacerbation of fatigue, or irritable bowel symptoms 1 person withdrew from the placebo group because of worsening fatigue			

No data from the following reference on this outcome. [58]

Further information on studies

Comment: **Clinical guide:**
We found insufficient evidence to recommend dietary supplements as a treatment in chronic fatigue syndrome.

OPTION EVENING PRIMROSE OIL

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- Evening primrose oil has not been studied in enough detail for us to draw conclusions on its efficacy.

Benefits and harms

Evening primrose oil versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT. [59]

Functional status

Compared with placebo Evening primrose oil seems no more effective at improving physical function at 3 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical function					
[59] RCT	50 people with CFS, Oxford criteria In review [34]	**Change in 15-point physical symptom score , 3 months** –1.5 with evening primrose oil (4 g daily) –1.0 with placebo Allocated treatments were given for 3 months	P = 0.54	⟷	Not significant

Overall improvement

Compared with placebo Evening primrose oil may be no more effective at increasing the proportion of people reporting an improvement at 3 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[59] RCT	50 people with CFS, Oxford criteria In review [34]	**Proportion of people reporting an improvement , 3 months** 29% with evening primrose oil (4 g daily) 46% with placebo Absolute numbers not reported Allocated treatments were given for 3 months	P = 0.09	⟷	Not significant

Quality of life

Compared with placebo Evening primrose oil seems no more effective at improving depressive symptoms at 3 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Depression					
[59] RCT	50 people with CFS, Oxford criteria In review [34]	**Change in depression scores (measured using the Beck Depression Inventory) , 3 months** –2.5 with evening primrose oil (4 g daily) –4.0 with placebo Allocated treatments were given for 3 months	P = 0.09	⟷	Not significant

Fatigue

No data from the following reference on this outcome. [59]

Adverse effects

No data from the following reference on this outcome. [59]

Further information on studies

Comment: We found one RCT (63 people) comparing evening primrose oil 4 g daily versus placebo in people with a diagnosis of post-viral fatigue syndrome. [60] This diagnosis was made on the basis of overwhelming fatigue, myalgia, and depression, which had been present for at least 1 year, and preceded by a febrile illness. At 3 months, significantly more people on active treatment reported improvement compared with placebo (33/39 [85%] with evening primrose oil *v* 4/24 [17%] with placebo; P <0.0001). The difference in outcome may be partly explained by participant selection: the study in people with CFS used currently accepted diagnostic criteria. [59] Also, whereas the RCT in people with post-viral fatigue syndrome used liquid paraffin as a placebo, [60] the CFS RCT

used sunflower oil, which is better tolerated and less likely to affect the placebo response adversely. [59]

Clinical guide:
There is insufficient evidence to recommend evening primrose oil as a treatment in CFS.

OPTION HOMEOPATHY

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- Homeopathy has not been studied in enough detail for us to draw conclusions on its efficacy.

Benefits and harms

Homeopathy versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT. [61]

Fatigue

Compared with placebo We don't know whether homeopathy is more effective at improving measures of fatigue (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
General fatigue					
[61] RCT	103 adults with CFS, Oxford criteria In review [34]	**Mean change in Multidimensional Fatigue Inventory (MFI) general fatigue subscale (self-reported) , 6 months** 2.70 with homeopathy 1.35 with placebo Allocated treatments were assessed over 6 months Various homeopathic remedies were assessed in the RCT; see further information on studies for full details	P = 0.04	○○○	homeopathy
Physical fatigue					
[61] RCT	103 adults with CFS, Oxford criteria In review [34]	**Mean change in MFI physical fatigue subscale , 6 months** 2.13 with homeopathy 1.28 with placebo Allocated treatments were assessed over 6 months Various homeopathic remedies were assessed in the RCT; see further information on studies for full details	P = 0.21	⟷	Not significant
Mental fatigue					
[61] RCT	103 adults with CFS, Oxford criteria In review [34]	**Mean change in MFI mental fatigue subscale , 6 months** 2.70 with homeopathy 2.05 with placebo Allocated treatments were assessed over 6 months Various homeopathic remedies were assessed in the RCT; see further information on studies for full details	P = 0.30	⟷	Not significant

Functional status

Compared with placebo Homeopathy seems no more effective at improving activity (assessed using the Multidimensional Fatigue Inventory reduced activity subscale) at 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Activity					
[61] RCT	103 adults with CFS, Oxford criteria In review [34]	**Mean change in Multidimensional Fatigue Inventory (MFI) reduced activity subscale , 6 months** 2.72 with homeopathy 1.81 with placebo Allocated treatments were assessed over 6 months Various homeopathic remedies were assessed in the RCT; see further information on studies for full details	P = 0.16	⟷	Not significant

Overall improvement

Compared with placebo Homeopathy seems no more effective at improving overall symptoms of chronic fatigue at 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[61] RCT	103 adults with CFS, Oxford criteria In review [34]	**Proportion of people with clinically significant improvement (defined as at least 3 points improvement on the 5 Multidimensional Fatigue Inventory [MFI] subscales) , 6 months** 11/43 (26%) with homeopathy 4/43 (9%) with placebo Allocated treatments were assessed over 6 months Various homeopathic remedies were assessed in the RCT; see further information on studies for full details	P = 0.09	⟷	Not significant

Quality of life

Compared with placebo Homeopathy seems no more effective at improving motivation (assessed using the Multidimensional Fatigue Inventory [MFI] reduced motivation subscale) at 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Motivation					
[61] RCT	103 adults with CFS, Oxford criteria In review [34]	**Mean change in Multidimensional Fatigue Inventory (MFI) reduced motivation subscale , 6 months** 1.35 with homeopathy 1.65 with placebo Allocated treatments were assessed over 6 months Various homeopathic remedies were assessed in the RCT; see	P = 0.82	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		further information on studies for full details			

Adverse effects

No data from the following reference on this outcome. [61]

Further information on studies

[61] As homeopathic prescribing methods are based on an assessment of the individual picture of illness, different homeopathic treatments were prescribed for different people within the RCT. The analysis was reported by intention to treat; however, people who failed to provide outcome measures were excluded.

Comment: **Clinical guide:**
There is insufficient evidence to recommend homeopathy as a treatment in chronic fatigue syndrome.

OPTION MAGNESIUM (INTRAMUSCULAR)

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- We don't know how effective intramuscular magnesium is in treating chronic fatigue syndrome.

Benefits and harms

Magnesium versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT. [62]

Fatigue

Compared with placebo Intramuscular magnesium injections may be more effective at improving energy at 6 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Energy					
[62] RCT	32 people with CFS, but not magnesium deficiency; Australian criteria In review [34]	**Mean change in Nottingham Health Profile energy score (change from baseline; decrease in score represents improvement) , 6 weeks** –51.04 with magnesium sulphate 50% (weekly im injections) –4.5 with placebo	P = 0.002	○○○	magnesium

No data from the following reference on this outcome. [62]

Overall improvement

Compared with placebo Intramuscular magnesium injections may be more effective at improving symptoms at 6 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[62] RCT	32 people with CFS, but not magnesium deficiency; Australian criteria In review [34]	**Proportion of people reporting overall benefit , 6 weeks** 12/15 (80%) with magnesium sulphate 50% (weekly im injections) 3/17 (18%) with placebo	RR 4.5 95% CI 1.6 to 13.1 NNT 2 95% CI 2 to 4	●●○	magnesium

Functional status

No data from the following reference on this outcome. [62]

Quality of life

No data from the following reference on this outcome. [62]

Adverse effects

No data from the following reference on this outcome. [62]

Further information on studies

[62] The RCT found that magnesium improved Nottingham Health Profile pain and emotional reaction subscale scores compared with placebo (mean change in score from baseline: pain subscale –19.63 with magnesium *v* +2.7 with placebo, P = 0.001; emotional reaction subscale –33.3 with magnesium *v* +7.4 with placebo, P = 0.013; score decrease represents improvement).

Comment: In the RCT, plasma and whole blood magnesium were normal, and only the red blood cell concentrations of magnesium were slightly lower than the normal range. [62] Three subsequent case-control studies have not found a deficiency of magnesium in people with CFS. [63] [64] [65] In these three studies, magnesium was in the normal range and no different from controls without CFS. However, none of the studies state how the normal range was established, so it is difficult to say whether they are equivalent.

Clinical guide:
There is no good evidence that intramuscular magnesium is of benefit in CFS.

OPTION NICOTINAMIDE ADENINE DINUCLEOTIDE (ORAL)

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- Oral nicotinamide adenine dinucleotide has not been studied in enough detail for us to draw conclusions on its efficacy.

Benefits and harms

Oral nicotinamide adenine dinucleotide versus placebo:

We found one systematic review (search date 2005), [34] which identified one poor-quality RCT. [66]

Overall improvement

Compared with placebo Oral nicotinamide adenine dinucleotide may be more effective at improving symptoms in people with chronic fatigue syndrome at 4 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[66] RCT **Crossover design**	35 people with CFS, CDC criteria In review [34]	**Proportion of people with 10% improvement on a self-devised 50-item symptom rating scale , 4 weeks** 8/26 (30%) with nicotinamide adenine dinucleotide (10 mg/day) 2/26 (8%) with placebo The RCT determined *a priori* that a 10% improvement in symptom scores was a meaningful improvement Analysis not by intention to treat; see further information on studies for details on follow-up	P <0.05 RCT had weak methods; see further information on studies for full details	○○○	nicotinamide adenine dinucleotide

Fatigue

No data from the following reference on this outcome. [66]

Functional status

No data from the following reference on this outcome. [66]

Quality of life

No data from the following reference on this outcome. [66]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[66] RCT **Crossover design**	35 people with CFS, CDC criteria In review [34]	**Adverse effects** with nicotinamide adenine dinucleotide (10 mg/day) with placebo The RCT reported minor adverse effects (loss of appetite, dyspep-			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		sia, and flatulence) associated with nicotinamide adenine dinucleotide, but no one stopped treatment as a result			

Further information on studies

[66] The RCT had several problems with its methods, including the use of inappropriate statistical analyses, the inappropriate exclusion of people from the analysis, and lack of numerical data preventing independent analysis of the published results. [67] Of the 35 people, two were excluded from the analysis for non-compliance and 7 were excluded for using psychotropic drugs.

Comment: **Clinical guide:**
There is no good evidence that oral nicotinamide adenine dinucleotide is of benefit in chronic fatigue syndrome compared with placebo.

OPTION PROLONGED REST

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- Prolonged rest has not been studied in enough detail for us to draw conclusions on its efficacy.

Benefits and harms

Prolonged rest:

We found no systematic review or RCTs of prolonged rest in people with chronic fatigue syndrome.

Further information on studies

Comment: It is not clear that evidence from people recovering from viral illness or in healthy volunteers can be extrapolated to people with chronic fatigue syndrome.

Clinical guide:
Although we found no RCTs of prolonged rest in people with chronic fatigue syndrome, historically it has been recommended as a treatment. However, indirect evidence suggests that prolonged rest may be ineffective and potentially harmful. We found observational evidence suggesting that prolonged inactivity may perpetuate or worsen fatigue, and is associated with symptoms in both healthy volunteers [68] and people recovering from viral illness. [69] [70]

OPTION GALANTAMINE

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- Based on a single large RCT, galantamine seems no better than placebo at improving symptoms of chronic fatigue syndrome.

Benefits and harms

Galantamine versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT comparing 4 different doses of galantamine hydrobromide versus placebo. [71]

Overall improvement

Compared with placebo Galantamine does not seem to increase symptomatic improvement at 16 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[71] RCT **5-armed trial**	434 people, aged 18 to 65 years, with CFS, CDC criteria; illness duration <7 years In review [34] The remaining arms evaluated galantamine 15 mg, galantamine 22.5 mg, and galantamine 30 mg	**Proportion of people classed as responding to treatment (reporting feeling "much improved" and "very much improved" on the Clinical Global Impression scale) , 16 weeks** 29% with galantamine 7.5 mg 18% with placebo Absolute numbers not reported The RCT had a high withdrawal rate (20%); however, its analysis included 97% (423/434) of people enrolled (last observation carried forward) The difference between galantamine and placebo was less than the prespecified level for clinical significance of 25%	Reported as not significant (galantamine 7.5 mg *v* placebo) P value not reported	⟷	Not significant
[71] RCT **5-armed trial**	434 people, aged 18 to 65 years, with CFS, CDC criteria; illness duration <7 years In review [34] The remaining arms evaluated galantamine 7.5 mg, galantamine 22.5 mg, and galantamine 30 mg	**Proportion of people classed as responding to treatment (reporting feeling "much improved" and "very much improved" on the Clinical Global Impression scale) , 16 weeks** 23% with galantamine 15 mg 18% with placebo Absolute numbers not reported The RCT had a high withdrawal rate (20%); however, its analysis included 97% (423/434) of people enrolled (last observation carried forward) The difference between galantamine and placebo was less than the prespecified level for clinical significance of 25%	Reported as not significant (galantamine 15 mg *v* placebo) P value not reported	⟷	Not significant
[71] RCT **5-armed trial**	434 people, aged 18 to 65 years, with CFS, CDC criteria; illness duration <7 years In review [34] The remaining arms evaluated galantamine 7.5 mg, galantamine 15 mg, and galantamine 30 mg	**Proportion of people classed as responding to treatment (reporting feeling "much improved" and "very much improved" on the Clinical Global Impression scale) , 16 weeks** 22% with galantamine 22.5 mg 18% with placebo Absolute numbers not reported The RCT had a high withdrawal rate (20%); however, its analysis included 97% (423/434) of people enrolled (last observation carried forward)	Reported as not significant (galantamine 22.5 mg *v* placebo) P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The difference between galantamine and placebo was less than the prespecified level for clinical significance of 25%			
[71] RCT **5-armed trial**	434 people, aged 18 to 65 years, with CFS, CDC criteria; illness duration <7 years In review [34] The remaining arms evaluated galantamine 7.5 mg, galantamine 15 mg, and galantamine 22.5 mg	**Proportion of people classed as responding to treatment (reporting feeling "much improved" and "very much improved" on the Clinical Global Impression scale) , 16 weeks** 20% with galantamine 30 mg 18% with placebo Absolute numbers not reported The RCT had a high withdrawal rate (20%); however, its analysis included 97% (423/434) of people enrolled (last observation carried forward) The difference between galantamine and placebo was less than the prespecified level for clinical significance of 25%	Reported as not significant (galantamine 30 mg *v* placebo) P value not reported	⟷	Not significant

Fatigue

No data from the following reference on this outcome. [71]

Functional status

No data from the following reference on this outcome. [71]

Quality of life

No data from the following reference on this outcome. [71]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[71] RCT **5-armed trial**	434 people, aged 18 to 65 years, with CFS, CDC criteria; illness duration <7 years In review [34]	**Withdrawal from RCT** 12/89 (13%) with galantamine 7.5 mg 20/86 (23%) with galantamine 15 mg 22/91 (24%) with galantamine 22.5 mg 22/86 (26%) with galantamine 30 mg	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		12/82 (15%) with placebo			

Further information on studies

[71] The RCT found no significant difference between galantamine and placebo in the proportion of people classed as "very much improved" (11% with 7.5 mg; 5% with 15 mg; 4% with 22.5 mg; 2% with 30 mg; and 4% with placebo; reported as not significant; P value not reported).

Comment: **Clinical guide:**
The evidence suggests that galantamine provides no meaningful benefit in people with chronic fatigue syndrome.

OPTION IMMUNOTHERAPY

- For GRADE evaluation of interventions for Chronic fatigue syndrome, see table, p 54 .
- Although there is some RCT evidence that immunotherapy can improve symptoms compared with placebo, it is associated with considerable adverse effects, and should therefore probably not be offered as a treatment for chronic fatigue.
- Immunoglobulin G is associated with considerable adverse effects, such as headache. Staphylococcus toxoid is associated with local reactions and can cause anaphylaxis.
- We found no clinically important results from RCTs about the effects of interferon alfa or aciclovir compared with placebo.

Benefits and harms

Immunoglobulin G versus placebo:

We found one systematic review (search date 2005), [34] which did not perform a meta-analysis or report quantified results from each study. The review identified 4 RCTs comparing immunoglobulin G versus placebo for 6 months. [72] [73] [74] [75]

Fatigue

Immunoglobulin G compared with placebo Immunoglobulin G may be no more effective at improving chronic fatigue severity at 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[72] RCT	30 people with CFS, CDC 1998 criteria In review [34]	**Percentage improvement in self-reported fatigue severity , 6 months** 0.0 with immunoglobulin G (1 g/kg; monthly iv injection) 14.3 with placebo (albumin)	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [73] [74] [75]

Functional status

Immunoglobulin G compared with placebo Immunoglobulin G may be no more effective at improving physical functioning at 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Physical functioning					
[72] RCT	30 people with CFS, CDC 1998 criteria In review [34]	**Mean change in short-form (SF)-36 physical functioning subscale , 6 months** –7.1 with immunoglobulin G (1 g/kg; monthly iv injection) –14.3 with placebo	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [73] [74] [75]

Overall improvement

Immunoglobulin G compared with placebo We don't know whether immunoglobulin G is more effective at improving overall symptoms of chronic fatigue (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[73] RCT	49 people with CFS, Australian criteria In review [34]	**Proportion of people with physician-rated improvement in symptoms and disability , 3 months after completion of treatment** 10/23 (44%) with immunoglobulin G (2 g/kg; monthly iv injection) 3/26 (12%) with placebo (iv maltose solution)	P = 0.03	○○○	immunoglobulin G
[74] RCT **4-armed trial**	99 people with CFS, Australian criteria In review [34]	**Improvement in median Karnofsky performance score , 6 months** 2.5 with low-dose immunoglobulin G (0.5 g/kg) 10 with medium-dose immunoglobulin G (1 g/kg) 5 with high-dose immunoglobulin G (2 g/kg) 7.5 with placebo (albumin)	P >0.13	⟷	Not significant
[75] RCT	71 adolescents aged 11 to 18 years with CFS, CDC criteria In review [34]	**Proportion of people reporting at least 25% improvement in mean functional outcome (assessed using the mean of clinician ratings from 4 areas of the participants' activities) , 6 months** 26/36 (72%) with immunoglobulin G (1 g/kg) 15/34 (44%) with placebo (maltose plus albumin solution) Treatments were given as 3 infusions 1 month apart	P <0.02	○○○	immunoglobulin G

No data from the following reference on this outcome. [72]

Quality of life

Immunoglobulin G compared with placebo We don't know whether immunoglobulin G is more effective at improving quality of life measures at 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[74] RCT **4-armed trial**	99 people with CFS, Australian criteria In review [34]	**Improvement in quality-of-life scores on visual analogue scales , 6 months** with low-dose immunoglobulin G (0.5 g/kg) with medium-dose immunoglobulin G (1 g/kg) with high-dose immunoglobulin G (2 g/kg) with placebo (albumin) Absolute results not reported	P >0.09	⟷	Not significant

No data from the following reference on this outcome. [72] [73] [75]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[72] RCT	30 people with CFS, CDC 1998 criteria In review [34]	**Headache** 14/15 (93%) with immunoglobulin G (1 g/kg; monthly iv injection) 9/15 (60%) with placebo Headache was the only adverse effect noted to be significantly different between groups; see further information on studies for details of other adverse effects	P = 0.03	○○○	placebo
[73] RCT	49 people with CFS, Australian criteria In review [34]	**Headache and worsening fatigue** 53/65 (82%) with immunoglobulin G (2 g/kg; monthly iv injection) 19/78 (24%) with placebo (iv maltose solution)	P <0.001	○○○	placebo
[73] RCT	49 people with CFS, Australian criteria In review [34]	**Phlebitis** 35/65 (54%) with immunoglobulin G (2 g/kg; monthly iv injection) 1/78 (1%) with placebo (iv maltose solution)	P <0.001	○○○	placebo
[74] RCT **4-armed trial**	99 adults with CFS, Australian criteria In review [34]	**Adverse effects (headaches, worsened fatigue, malaise, and concentration impairment)** 18/22 (82%) with immunoglobulin G (0.5 g/kg) 20/28 (71%) with immunoglobulin G (1 g/kg) 18/23 (78%) with immunoglobulin G (2 g/kg) 23/26 (88%) with placebo	P = 0.49	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[75] RCT	71 adolescents aged 11 to 18 years with CFS, CDC criteria In review [34]	**Severe headache after first infusion** 64% with immunoglobulin G (1 g/kg) 20% with placebo (maltose plus albumin solution) Absolute numbers not reported	P <0.01	○○○	placebo

Interferon alfa versus placebo:

We found one systematic review (search date 2005), [34] which identified two RCTs comparing interferon alfa versus placebo. [76] [77] The first RCT (30 people with CFS, Oxford criteria, crossover design) identified by the review only found treatment benefit on subgroup analysis of people with diminished natural killer cell function but normal lymphocyte proliferation. In the active treatment group, 2/13 (15%) people developed neutropenia. [76] The second RCT (20 people with CFS, crossover design) identified by the review did not present results in a manner that allowed clear interpretation of treatment effect. [77]

Staphylococcus toxoid versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT. [78]

Overall improvement

Staphylococcus toxoid compared with placebo Staphylococcus toxoid may be more effective at improving overall symptoms (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall improvement					
[78] RCT	100 women who met both the American Cancer Society criteria for fibromyalgia and the CDC criteria for CFS and had functional impairment lasting >6 months In review [34]	**Proportion of people reporting feeling "minimally improved", "much improved", or "very much improved" on Clinical Global Impression scale , 26 weeks** 32/49 (65%) with staphylococcus toxoid (subcutaneous injection; dose increased weekly from 0.1 mL to 1.0 mL, followed by 1.0 mL doses every 4 weeks) 9/49 (18%) with placebo	P <0.001	○○○	staphylococcus toxoid

Fatigue

No data from the following reference on this outcome. [78]

Functional status

No data from the following reference on this outcome. [78]

Quality of life

No data from the following reference on this outcome. [78]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[78] RCT	100 women who met both the American Cancer Society criteria for fibromyalgia and the CDC criteria for CFS and had functional impairment lasting >6 months In review [34]	**Overall adverse effects (excluding local reactions)** 13/49 (26%) with staphylococcus toxoid (subcutaneous injection; dose increased weekly from 0.1 mL to 1.0 mL, followed by 1.0 mL doses every 4 weeks) 7/49 (14%) with placebo All those receiving staphylococcus toxoid had a local reaction at the injection site	P = 0.14	⟷	Not significant

Aciclovir versus placebo:

We found one systematic review (search date 2005), [34] which identified one crossover RCT (27 people) [79] comparing aciclovir versus placebo.

Fatigue

Aciclovir compared with placebo We don't know how effective aciclovir is compared with placebo at improving fatigue (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[79] RCT **Crossover design**	27 people with CFS (CDC criteria), mean age 34.1 years In review [34] Participants also had to have persisting antibodies to Epstein–Barr virus early antigens (titres greater-than or equal to 1:40) or undetectable levels of antibodies to Epstein–Barr virus nuclear antigens (titres <1:2) or both	**Fatigue (Profile of Mood States questionnaire)** with aciclovir with placebo Absolute results not reported Intervention consisted of intravenous placebo or aciclovir (500 mg per square metre of body-surface area) administered every 8 hours for 7 days. The same drug was then given orally for 30 days (aciclovir, 800 mg 4 times daily). There were 6-week observation periods before, between, and after the treatments	Mean difference 1.26 P = 0.27 Post-crossover results (pre-crossover results not reported by study)	⟷	Not significant

Overall improvement

No data from the following reference on this outcome. [79]

Functional status

No data from the following reference on this outcome. [79]

Quality of life

No data from the following reference on this outcome. [79]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[79] RCT **Crossover design**	27 people with CFS (CDC criteria), mean age 34.1 years In review [34] Participants also had to have persisting antibodies to Epstein–Barr virus early antigens (titres greater-than or equal to 1:40) or undetectable levels of antibodies to Epstein–Barr virus nuclear antigens (titres <1:2) or both	**Adverse effects** with aciclovir with placebo Absolute results not reported Intervention consisted of intravenous placebo or aciclovir (500 mg per square metre of body-surface area) administered every 8 hours for 7 days. The same drug was then given orally for 30 days (aciclovir, 800 mg 4 times daily). There were 6-week observation periods before, between, and after the treatments.	Significance not reported although RCT reported more adverse effects occurred in the aciclovir treatment phase and more adverse effects occurred in the intravenous phases of treatment than in the oral phases Post-crossover results (pre-crossover results not reported by study) See further information on studies for further details of adverse effects		

Dialysable leukocyte extract versus placebo:

We found one systematic review (search date 2005), [34] which identified one RCT evaluating immunological therapy (dialysable leukocyte extract, DLE) and placebo using a factorial design. [26]

Fatigue

Dialysable leukocyte extract (DLE) compared with placebo We don't know how effective DLE is compared with placebo at improving fatigue (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fatigue					
[26] RCT **4-armed trial**	90 people with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms reported on	**Mean fatigue score (profile of mood states subscale) , 7 months (3 months after completion of treatment)** 16.9 with DLE 17.3 with placebo 47 people in this analysis	Statistical significance not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	CBT plus dialysable leukocyte extract (DLE) and CBT plus placebo	Treatment was with 8 biweekly injections of DLE or placebo (lyophilised normal saline)			

Functional status

Dialysable leukocyte extract (DLE) compared with placebo We don't know how effective DLE is compared with placebo at improving functional status (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Functional status					
[26] RCT **4-armed trial**	90 people with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms reported on CBT plus dialysable leukocyte extract (DLE) and CBT plus placebo	**Mean number of non-sedentary hours , 7 months (3 months after completion of treatment)** 4.9 with DLE 5.2 with placebo 47 people in this analysis Treatment was with 8 biweekly injections of DLE or placebo (lyophilised normal saline)	Statistical significance not reported		
[26] RCT **4-armed trial**	90 people with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms reported on CBT plus DLE and CBT plus placebo	**Mean score for ability to participate in daily activities (Karnofsky performance score) , 7 months (3 months after completion of treatment)** 74.8 with DLE 73.4 with placebo 47 people in this analysis Treatment was with 8 biweekly injections of DLE or placebo (lyophilised normal saline)	Statistical significance not reported		

Overall improvement

No data from the following reference on this outcome. [26]

Quality of life

Dialysable leukocyte extract (DLE) compared with placebo We don't know how effective DLE is compared with placebo at improving quality of life (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[26] RCT **4-armed trial**	90 people with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined)	**Mean visual analogue score , 7 months (3 months after completion of treatment)** 498 with DLE 477 with placebo	Statistical significance not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [34] The remaining 2 arms reported on CBT plus dialysable leuko-cyte extract (DLE) and CBT plus placebo	47 people in this analysis Treatment was with 8 biweekly injections of DLE or placebo (lyophilised normal saline)			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[26] RCT **4-armed trial**	90 people with a mean age of 39.6 years who fulfilled diagnostic criteria for CFS (not further defined) In review [34] The remaining 2 arms reported on CBT plus dialysable leuko-cyte extract (DLE) and CBT plus placebo	**Number of people with minor discomfort at injection site (with 1 or more injection) , 7 months (3 months after comple-tion of treatment)** with DLE with placebo Treatment was with 8 biweekly injections of DLE or placebo (lyophilised normal saline)	Adverse effects data pooled from all 4 trial arms for all participants who received DLE (45 people) versus all who received placebo (43 people). Significantly more people suffered minor discomfort at the injection site with DLE than with placebo	○○○	DLE

Dialysable leukocyte extract versus CBT:

We found one systematic review (search date 2005), [34] which identified one RCT evaluating CBT and immunological therapy (dialysable leukocyte extract, DLE) using a factorial design. [26] See option on CBT, p 3 .

Further information on studies

[72] The RCT found that placebo significantly improved social function compared with immunoglobulin G (dichotomous figures and P value not reported). **Adverse effects** Adverse effects judged to be worse than symptoms before treatment in either group included gastrointestinal complaints (18 people), headaches (23 people), myalgia or arthralgia (6 people), and fever (10 people). Three people in each group had major adverse effects, and one person in each group withdrew from the trial as a consequence. Comparative data for these adverse effects not reported.

[79] The RCT reported on adverse effects including nausea, diarrhoea, vomiting, headache, dizziness, jitteriness, rash, and reversible renal failure; all of which were higher with aciclovir treatment. The statistical significance was not reported for any of the adverse effects other than gastrointestinal side effects, which were significantly higher with aciclovir treatment. Three people had reversible renal failure with aciclovir infusions and were subsequently withdrawn from the study.

Comment: **Clinical guide:**
Given the weak evidence of benefit for immunotherapy, the potential harms indicate that it should not be offered as a treatment for CFS.

GLOSSARY

Beck Depression Inventory Standardised scale to assess depression. This instrument consists of 21 items to assess the intensity of depression. Each item is a list of 4 statements (rated 0, 1, 2, or 3), arranged in increasing severity, about a particular symptom of depression. The range of scores possible are 0 = least severe depression to 63 = most severe depression. It is recommended for people aged 13 to 80 years. Scores of more than 12 or 13 indicate the presence of depression.

Chronic fatigue syndrome, Australian definition (1) Chronic persisting or relapsing fatigue of a generalised nature, exacerbated by minor exercise, causing significant disruption of usual daily activities, and present for more than 6 months; (2) Neuropsychiatric dysfunction including impairment of concentration evidenced by difficulty in completing mental tasks that were easily accomplished before the onset of the syndrome; new onset of short-term memory impairment; (3) No alternative diagnosis reached by history, physical examination, or investigations over a 6-month period. [3]

Clinical Global Impression Scale A one-item, observer-rated scale for measuring the severity of a condition. It has been investigated for validity and reliability. The scale is scored from 0 (not ill at all) to 7 (severely ill).

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Karnofsky score Is a measure of performance status based on physical ability (scale 0–100). 100: normal, no complaints or evidence of disease; 90: able to perform normal activity, minor signs and symptoms of disease; 80: able to perform normal activity with effort, some signs and symptoms of disease; 70: cares for self, unable to perform normal activity or to do active work; 60: requires occasional assistance but is able to care for most of own needs; 50: requires considerable assistance and frequent medical care; 40: requires special care and assistance, disabled; 30: hospital admission indicated, although death not imminent, severely disabled; 20: hospital admission necessary, active supportive treatment required, very sick; 10: fatal processes progressing rapidly, moribund; 0: death.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

CBT New evidence added. [25] [31] Categorisation unchanged (Beneficial).

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Disclaimer

TABLE 1 **Diagnostic criteria for chronic fatigue syndrome (see text).**

CDC 1994 [1]	Oxford, UK [2]
Clinically evaluated, medically unexplained fatigue of at least 6 months' duration that is:	Severe, disabling fatigue of at least 6 months' duration that:
– of new onset	– affects both physical and mental functioning
– not a result of ongoing exertion	– was present for more than 50% of the time
– not substantially alleviated by rest	
– a substantial reduction in previous levels of activity	
The occurrence of 4 or more of the following symptoms:	Other symptoms, particularly myalgia, sleep and mood disturbance, may be present
– subjective memory impairment	
– tender lymph nodes	
– muscle pain	
– joint pain	
– headache	
– unrefreshing sleep	
– postexertional malaise (greater than 24 hours)	
Exclusion criteria	
– active, unresolved, or suspected disease likely to cause fatigue	– active, unresolved, or suspected disease likely to cause fatigue
– psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)	– psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)
– psychotic disorders	– psychotic disorders
– dementia	– dementia
– anorexia or bulimia nervosa	– anorexia or bulimia nervosa
– alcohol or other substance misuse	
– severe obesity	

CDC, US Centers for Disease Control and Prevention.

GRADE **Evaluation of interventions for Chronic fatigue syndrome.**

Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
Important outcomes			**Fatigue, Functional status, Overall improvement, Quality of life**						
What are the effects of treatments for chronic fatigue syndrome?									
5 (704) [25] [26] [29] [30] [32] [31]	Fatigue	CBT versus control interventions	4	–3	0	0	0	Very low	Quality points deducted for poor follow-up, flaws in analysis, and incomplete reporting of results
5 (486) [25] [26] [28] [30] [31] [32]	Functional status	CBT versus control interventions	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for inclusion of multiple comparisons with no statistical adjustment
1 (60) [33]	Overall improvement	CBT versus control interventions	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (303) [26] [27] [30]	Quality of life	CBT versus control interventions	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (90) [26] [34]	Fatigue	CBT versus dialysable leukocyte extract	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (90) [26] [34]	Functional status	CBT versus dialysable leukocyte extract	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (90) [26] [34]	Quality of life	CBT versus dialysable leukocyte extract	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (257) [39] [40] [41]	Fatigue	Graded exercise therapy versus control interventions	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (66) [39]	Functional status	Graded exercise therapy versus control interventions	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (176) [39] [41] [42]	Overall improvement	Graded exercise therapy versus control interventions	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
1 (61) [41]	Quality of life	Graded exercise therapy versus control interventions	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for control including active relaxation
1 (148) [43]	Fatigue	Graded exercise therapy plus education versus written information alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (148) [43]	Functional status	Graded exercise therapy plus education versus written information alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (243) [40] [44]	Fatigue	Fluoxetine versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for statistical heterogeneity in studies
2 (243) [40] [44]	Quality of life	Fluoxetine versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for uncertainty of clinical importance of result in 1 RCT and for combined analysis (includes an active intervention; graded aerobic exercise) in 1 RCT

Important outcomes			Fatigue, Functional status, Overall improvement, Quality of life						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (30) [45]	Overall improvement	Phenelzine versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
1 (90) [46]	Overall improvement	Moclobemide versus placebo	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for OR >2
1 (40) [47]	Overall improvement	Sertraline versus clomipramine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (25) [50]	Fatigue	Fludrocortisone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (100) [49]	Overall improvement	Fludrocortisone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (25) [50]	Functional status	Fludrocortisone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (32) [52]	Fatigue	Hydrocortisone versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (65) [51]	Functional status	Hydrocortisone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (65) [51]	Overall improvement	Hydrocortisone versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (65) [51]	Quality of life	Hydrocortisone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (100) [53]	Fatigue	Hydrocortisone plus fludrocortisone versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, methodological flaws, and incomplete reporting of results
3 (at least 128) [56] [58]	Fatigue	Dietary supplements versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (at least 57) [56]	Functional status	Dietary supplements versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (50) [59]	Functional status	Evening primrose oil versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (50) [59]	Overall improvement	Evening primrose oil versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and for incomplete reporting of results
1 (50) [59]	Quality of life	Evening primrose oil versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (103) [34]	Fatigue	Homeopathy versus placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
1 (103) [61]	Functional status	Homeopathy versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (103) [61]	Overall improvement	Homeopathy versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (103) [61]	Quality of life	Homeopathy versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (32) [62]	Fatigue	Magnesium versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and inclusion of people with normal magnesium levels
1 (32) [62]	Overall improvement	Magnesium versus placebo	4	–2	0	0	+1	Moderate	Quality points deducted for sparse data and inclusion of people with normal magnesium levels. Effect-size point added for RR >2
1 (35) [66]	Overall improvement	Oral nicotinamide adenine dinucleotide versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results

Important outcomes			Fatigue, Functional status, Overall improvement, Quality of life						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (434) [71]	Overall improvement	Galantamine versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (30) [72]	Fatigue	Immunoglobulin G versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (30) [72]	Functional status	Immunoglobulin G versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (219) [73] [74] [75]	Overall improvement	Immunoglobulin G versus placebo	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for different diagnostic criteria
1 (99) [74]	Quality of life	Immunoglobulin G versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (100) [78]	Overall improvement	Staphylococcus toxoid versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria
1 (27) [79]	Fatigue	Aciclovir versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for narrow inclusion criteria
1 (90) [26] [34]	Fatigue	Dialysable leukocyte extract versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (90) [26] [34]	Functional status	Dialysable leukocyte extract versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (90) [26] [34]	Quality of life	Dialysable leukocyte extract versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.